(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
31 December 2003 (31.12.2003)

PCT

(10) International Publication Number
WO 2004/000317 A1

(51) International Patent Classification[7]: A61K 31/445, A61P 25/28

(21) International Application Number: PCT/SI2003/000019

(22) International Filing Date: 18 June 2003 (18.06.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
P-200200155 19 June 2002 (19.06.2002) SI

(71) Applicant *(for all designated States except US)*: **KRKA TOVARNA ZDRAVIL, D.D., NOVO MESTO** [SI/SI]; Smarjeska c. 6, 8501 Novo mesto (SI).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **VRBINC, Miha** [SI/SI]; Gotna vas 20, 8000 Novo mesto (SI). **PUNCUH KOLAR, Alesa** [SI/SI]; Resljeva 5, 8311 Kostanjevica na Krki (SI). **VRECER, Franc** [SI/SI]; Potok 5b, 8351 Straza pri Novem mestu (SI). **KOTAR JORDAN, Berta** [SI/SI]; Vodeniska 19, 8311 Kostanjevica na Krki (SI). **STANGELJ, Veronika** [SI/SI]; Stopice 61, 8322 Stopice (SI).

(74) Agent: **PATENTNA PISARNA D.O.O.**; Copova 14, POB 1725, 1001 Ljubljana (SI).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2004/000317 A1

(54) Title: PHARMACEUTICAL COMPOSITION CONTAINING STABILISED AMORPHOUS FORM OF DONEPEZIL HYDROCHLORIDE

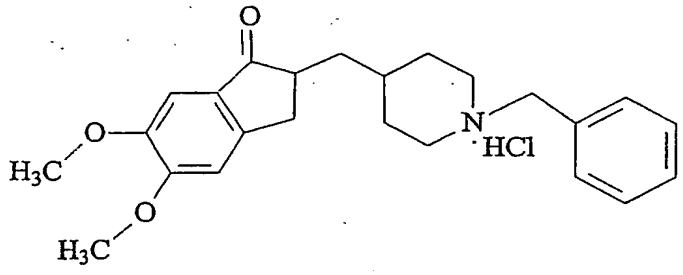
(57) Abstract: The present invention relates to stabilised pharmaceutical compositions with an amorphous form of 1-benzyl-4-((5,6-dimethoxy-1-indanon)-2-yl)methyl-piperidine (donepezil) hydrochloride and to a process for the stabilisation of this compound. The pharmaceutical composition is prepared by in situ formation of donepezil hydrochloride and loading the obtained solution onto a mixture of pharmaceutically acceptable excipients. The amorphous form of donepezil hydrochloride is stabilised by adding a crystallization inhibitor to the solution or to the mixture of pharmaceutically acceptable excipients.

PHARMACEUTICAL COMPOSITION CONTAINING STABILISED AMORPHOUS FORM OF DONEPEZIL HYDROCHLORIDE

The present invention relates to a stable pharmaceutical composition containing 1-benzyl-4-((5,6-dimethoxy-1-indanon)-2-yl)methyl-piperidine (donepezil) hydrochloride and to a method for the stabilisation of this compound.

Technical Field of the Invention

Donepezil hydrochloride is a well-known medicinal active ingredient with a strong and highly selective acetylcholinesterase inhibition and is identified by the following chemical formula:



Donepezil is described to be effective in the treatment and/or prevention of various diseases such as senile dementia, particularly senile dementia of Alzheimer's type, cerebrovascular diseases accompanying cerebral apoplexy, e.g. cerebral haemorrhages or cerebral infarct, cerebral arteriosclerosis, head injuries and other diseases. It is also used in the treatment and/or prevention of aprosexia, speech disorders, hypobulia, mood changes, attention deficit hyperreactivity disorders, recent memory disturbances, hallucinatory-paranoid syndrome, behaviour changes and other similar diseases accompanying encephalitis, cerebral palsy and others.

Prior Art

Various processes for the synthesis of donepezil and/or compositions with donepezil as a medicinal active ingredient have been described.

WO 97/46527 describes a method for the preparation of polymorphs I-V and of an amorphous form of donepezil hydrochloride. The amorphous form is prepared in such a way that donepezil hydrochloride is dissolved in water, the solution is cooled to a low temperature and freeze-dried for 4 days at the temperature -82°C. When comparing the results of stability testing it was established that the polymorphs I-IV are preferred over the amorphous form because they show enhanced chemical stability. Thus, the amorphous form is less stable when compared with the polymorphs I-IV. After a three-week exposal to the temperature of 80°C, the content of impurities rose from 0.12% at time 0 (zero) to 3.29%. Further, in hygroscopicity testing it was found that the amorphous form is significantly more hygroscopic when exposed to different relative humidities as compared to polymorphs I-IV. At the exposure of the amorphous form to a 100.0 % relative humidity, the water content rose from initial 2.03% to 15.44%.

EP-A-1 086 706 describes the preparation of donepezil in salt form to enhance stability. In order to achieve a higher stability the use of organic acids is suggested to be preferred over hydrochloric acid, since the use of the latter yields a higher amount of impurities. When 5 mg of hydrochloric acid were added to 5 mg/5 ml of donepezil solution and it was stored at 60°C for one month, the ratio of the area of impurities on the chromatogram was 0.42%. In a second experiment, wherein 5 mg of hydrochloric acid were added to 5 mg/5 ml of donepezil solution containing 10% of povidone and stored at the same conditions (60°C, one month), the ratio of the area of impurities on a chromatogram was 2.45%.

EP-A-1 120 109 describes the use of steam-extruded polymers for enhancing the disintegration and dissolution of a pharmaceutical composition. Although an amorphous form is described in this document, the rapid disintegration was achieved by the use of steam-extruded polymers.

According to the literature data, amorphous forms are generally more hygroscopic and less stable than crystalline forms and crystallize into a crystalline form or a mixture of crystalline forms (Brittain HG. Polymorphism in Pharmaceutical Solids. 1st ed. New York: Marcel Dekker, 1999). Amorphous substances may be stabilised by the addition of crystallization inhibitors (Chem. Pharm. Bull. 1983; 31 (7): 2510-2512).

Technical Problem

Considering all the facts described in the prior art, there existed a need to prepare a stable formulation containing the amorphous form of donepezil hydrochloride. This problem was solved by preparing donepezil hydrochloride *in situ* and stabilizing the amorphous form by the addition of a crystallization inhibitor.

Detailed Description of the Invention

An object of the present invention is a pharmaceutical composition containing amorphous or stabilised amorphous donepezil hydrochloride, which composition is obtained by preparing donepezil hydrochloride *in situ* and by adding a crystallization inhibitor.

A process for the preparation of a pharmaceutical composition containing donepezil hydrochloride comprises the following steps:

a) dispersing donepezil in a pharmaceutically acceptable solvent and adding a hydrochloric acid solution to the dispersion,

or *vice versa*, adding donepezil to a hydrochloric acid solution in a pharmaceutically acceptable solvent, and

b) loading the obtained solution onto a mixture of pharmaceutically acceptable carriers.

The crystallization inhibitor/s can be added either to the solution obtained under a) or to the mixture of pharmaceutically acceptable carriers under b).

A further object of the present invention is the preparation of the amorphous form of donepezil hydrochloride by spray-drying a donepezil hydrochloride solution. The solution of donepezil hydrochloride can be prepared either *in situ* by adding a hydrochloric acid solution to a dispersion of donepezil, or *vice versa*, by dissolving donepezil in hydrochloric acid or by dissolving donepezil hydrochloride in a pharmaceutically acceptable solvent or a mixture of solvents.

Optionally, the amorphous form of donepezil hydrochloride can be stabilised by dissolving a crystallization inhibitor in a solution of donepezil hydrochloride, whereupon the solvent is removed by spray-drying. Subsequently, the amorphous form or the stabilised amorphous form of donepezil hydrochloride can be dissolved in a pharmaceutically acceptable solvent and further processed by loading the obtained solution onto a mixture of pharmaceutically acceptable excipients. The dry amorphous form or the stabilised dry amorphous form of donepezil hydrochloride can be admixed to pharmaceutically acceptable excipients so as to prepare a pharmaceutical composition.

The solution of donepezil hydrochloride prepared *in situ* or by dissolving the amorphous form or the stabilised amorphous form of donepezil hydrochloride, can be loaded onto pharmaceutically acceptable carriers such as a powdered mixture of excipients, pellets, crystals, granules (e.g. granulated excipients), microtablets, tablets.

The final pharmaceutical dosage forms can be formulated by known methods such as wet or dry granulation, direct tabletting, pelletisation.

The conventional equipment used for manufacturing pharmaceutical compositions can be a high shear mixer/granulator, Wurster coating system, fluid bed granulator (top spray, bottom spray, tangential spray), conventional coating pans etc.

The pharmaceutical composition can be in any conventional pharmaceutical unit dosage form such as granules, pellets, tablets, film-coated tablets, fast dispersible tablets, capsules etc.

According to the present invention, the crystallization inhibitor is selected from at least one of cellulose derivatives, polyvinylpyrrolidone and derivatives thereof, xanthan gums, pectins, alginates, tragacanth and derivatives, gum arabic and derivatives, carrageenans, agar and derivatives, polysaccharides from microbiological sources, arabinogalactanes, galactomannans, dextrans and the like. The preferred crystallization inhibitors are cellulose derivatives and polyvinylpyrrolidone and its derivatives.

The crystallization inhibitor is added in an amount from 0.0001 g to 5.0 g for 1 g of donepezil hydrochloride, preferably between 0.5 g to 2.0 g.

The solution is prepared by the addition of donepezil to hydrochloric acid in a molar ratio of 1 : 0.5-5, preferably in a molar ratio of 1:0.5–3. The pH value of the solution obtained is between 2 and 6, preferably between 3.0 to 5.5.

The pharmaceutically acceptable solvents are water, a mixture of water with water-miscible solvents, acetone, alcohols such as ethanol, methanol, isopropanol, preferably water or a mixture of water with alcohols, or alcohols.

The pharmaceutically acceptable excipients can be diluents such as microcrystalline cellulose, lactose (anhydrous or in monohydrate form), other sugars such as mannitol, saccharose or a mixture thereof, siliconised microcrystalline cellulose, calcium hydrogen phosphate; binders such as povidone, microcrystalline cellulose, hydroxy-ethylcellulose, hydroxypropylcellulose, hypromellose, starch, pregelatinised starch; disintegrants such as maize starch, sodium starch glycolate, crospovidone, microcrystalline cellulose, carboxymethylcellulose sodium, Amberlite®; lubricants such as magnesium stearate, calcium stearate, sodium laurylsulphate, hydrogenated vegetable oil, hydrogenated castor oil, sodium stearyl fumarate.

The method according to the present invention is advantageous over the known prior art in that, unexpectedly and surprisingly, a highly stable amorphous form of donepezil hydrochloride with a low content of impurities in the pharmaceutical composition is obtained. The results of the stability testing of the pharmaceutical compositions with the amorphous form according to the present invention are presented in Table 1.

Table 1

Time of exposure to air at 40°C/75% RH; (days)	Total amount of related substances (%)
0	0.05
28	0.09

The present invention is illustrated by the following Examples without being limited thereto.

Example 1

Preparation of tablets

Donepezil (20 g) was dispersed in a pre-prepared aqueous solution (240 ml) containing concentrated hydrochloric acid (4 ml) and povidone (20 g). Lactose monohydrate (294 g), microcrystalline cellulose (200 g), maize starch (30 g) and hydroxyethylcellulose (15 g) were passed through a 30-mesh sieve and subsequently mixed in a fluid bed granulator.

The aqueous solution of donepezil hydrochloride to be granulated was sprayed onto the powder mixture in the fluid-bed granulator and after the completed spraying the obtained granulate was dried in a fluid-bed dryer at an inlet temperature of 60°C. The dried granulate was passed through an 18-mesh sieve and mixed with maize starch (30 g) and magnesium stearate (3 g) in a biconic mixer.

The mixture to be tabletted (the granulate with added maize starch and magnesium stearate) was compressed into tablets, each containing 5 mg of donepezil hydrochloride. The average weight of the tablets was 140 mg.

Example 2

Preparation of tablets

Donepezil (20 g) was dispersed in a pre-prepared aqueous solution (240 ml) containing 0.5 M hydrochloric acid (35 ml). The thus prepared aqueous solution of donepezil hydrochloride was admixed with an aqueous solution containing hypromellose (10 g). Microcrystalline cellulose (262 g), lactose monohydrate (262 g) and maize starch (25 g) were passed through a 30-mesh sieve and subsequently mixed in a fluid-bed granulator.

The aqueous solution of donepezil hydrochloride was sprayed onto the powder mixture in the fluid-bed granulator and the obtained granulate was then dried in a fluid-bed dryer at an inlet temperature of 70°C. The dried granulate was passed through an 18-mesh sieve and mixed with maize starch (30 g) and hydrogenated vegetable oil (3 g) in a biconic mixer.

The mixture to be tabletted (the granulate with admixed maize starch and hydrogenated castor oil) was compressed into tablets, each containing 5 mg of donepezil hydrochloride. The average weight of the tablets was 140 mg.

Example 3

Preparation of tablets

Donepezil (30 g) was dispersed in purified water (320 g). During a fast stirring of the dispersion, concentrated hydrochloric acid (6 ml) was slowly added. A mixture of lactose monohydrate (818 g), crospovidone (40 g) and povidone (25 g) was passed through a 30-mesh sieve and subsequently mixed in a fluid-bed granulator.

The aqueous solution of donepezil hydrochloride to be granulated was sprayed onto the powder mixture in the fluid-bed granulator and the obtained granulate was then dried in a fluid-bed dryer at an inlet temperature of 60°C. The dried granulate was passed through an 18-mesh sieve and mixed with magnesium stearate (5 g) in a biconic mixer.

The mixture to be tabletted (the granulate with admixed magnesium stearate) was compressed into tablets, each containing 10 mg of donepezil hydrochloride. The average weight of the tablets was 280 mg.

Example 4

Preparation of cores

Donepezil (34 g) was dispersed in purified water (360 g). During a fast stirring of the dispersion, concentrated hydrochloric acid (7 ml) was slowly added. Lactose monohydrate (605 g), microcrystalline cellulose (231 g), maize starch (50 g) and hydroxypropylcellulose (30 g) were passed through a 30-mesh sieve and subsequently mixed in a fluid-bed granulator.

The aqueous solution of donepezil hydrochloride (pH = 4.5) to be granulated was sprayed onto the powder mixture in the fluid-bed granulator and the obtained granulate was then dried in a fluid-bed dryer at an inlet temperature of 70°C. The dried granulate was passed through an 18-mesh sieve and admixed with maize starch (50 g) and magnesium stearate (5 g) in a biconic mixer.

The mixture to be tabletted (the granulate with admixed maize starch and magnesium stearate) was compressed into cores, each containing 10 mg of donepezil hydrochloride. The average weight of the cores was 280 mg.

Preparation of film-coated tablets

The obtained cores were coated with a conventional ready-to-make mixture for the preparation of a film-coating suspension containing hydroxypropylmethylcellulose, macrogol 400, iron oxide yellow and titanium dioxide, until the average weight of the film coated tablets was 288 mg.

The pH value of film coated tablets dispersed in purified water was 6.4.

Example 5

Preparation of tablets

Donepezil (300 g) was dispersed in purified water (300 g). During a fast stirring of the dispersion 0.5 M hydrochloric acid (520 ml) was slowly added. The aqueous solution of donepezil hydrochloride was spray-dried on a mini spray-dryer Büchi 190.

Amorphous donepezil hydrochloride (100 g) was dissolved in purified water (1000 ml). Hydroxypropylcellulose (85 g), lactose monohydrate (1680 g), microcrystalline cellulose (640 g) and maize starch (140 g) were passed through a 30-mesh sieve.

The aqueous solution of donepezil hydrochloride to be granulated was sprayed onto the powder mixture in a fluid-bed granulator and the obtained granulate was then dried in a fluid-bed dryer at an inlet temperature of 65°C. The dried granulate was passed through an 18-mesh sieve and admixed with maize starch (140 g) and magnesium stearate (15 g) in a biconic mixer.

The mixture to be tabletted (the granulate with admixed maize starch and magnesium stearate) was compressed into tablets, each containing 5 mg of donepezil hydrochloride. The average weight of the tablets was 140 mg.

Example 6

Preparation of cores

Donepezil (300 g) was dispersed in purified water (300 g). During a fast stirring of the dispersion, 0.5 M hydrochloric acid (520 ml) was slowly added. Separately, povidone (329 g) was dissolved in purified water (1200 ml). Both solutions were mixed together in such a manner that the aqueous solution of donepezil hydrochloride was added to

the solution of povidone. The aqueous solution obtained was spray-dried on a mini spray-dryer Büchi 190.

Amorphous donepezil hydrochloride (50 g) stabilised with povidone (50 g) was dissolved in purified water (1000 ml). Hydroxypropylcellulose (42 g), lactose monohydrate (790 g), microcrystalline cellulose (320 g) and maize starch (70 g) were passed through a 30-mesh sieve.

The aqueous solution of donepezil hydrochloride to be granulated was sprayed onto the powder mixture in a fluid-bed granulator and the obtained granulate was then dried in a fluid-bed dryer at an inlet temperature of 65°C. The dried granulate was passed through an 18-mesh sieve and admixed with maize starch (70 g) and magnesium stearate (8 g) in a biconic mixer.

The mixture to be tabletted (the granulate with admixed maize starch and magnesium stearate) was compressed into cores, each containing 5 mg of donepezil hydrochloride. The average weight of the cores was 140 mg.

Preparation of film coated tablets

The obtained cores were coated with a conventional ready-to-make mixture for the preparation of a film-coating suspension containing hydroxypropylmethylcellulose, macrogol 400 and titanium dioxide, until the average weight of the film coated tablets was 144 mg.

Claims

1. Pharmaceutical composition with donepezil hydrochloride containing an amorphous form or stabilised amorphous form thereof, characterized in that it is manufactured by preparing donepezil hydrochloride *in situ* and by adding a crystallization inhibitor.

2. Pharmaceutical composition according to claim 1, characterized in that the crystallization inhibitor is selected from at least one of cellulose derivatives, polyvinylpyrrolidone and derivatives thereof, xanthan gums, pectins, alginates, tragacanth and derivatives, gum arabic and derivatives, carrageenans, agar and derivatives, polysaccharides from microbiological sources, arabinogalactanes, galactomannans, dextrans.

3. Pharmaceutical composition according to claims 1 or 2, characterized in that the crystallization inhibitor is added in an amount from 0.0001g to 5.0 g for 1 g of donepezil hydrochloride.

4. A process for the preparation of a pharmaceutical composition according to any of the claims 1 to 3 comprising the steps:
   a) dispersing donepezil in a pharmaceutically acceptable solvent and adding a hydrochloric acid solution to the dispersion,
      or *vice versa*, adding donepezil to a hydrochloric acid solution in a pharmaceutically acceptable solvent, and
   b) loading the obtained solution onto a mixture of pharmaceutically acceptable carriers.

5. A process according to claim 4, characterized in that the crystallization inhibitor is added either to the solution obtained or to the mixture of pharmaceutically acceptable excipients.

6. A process according to claim 4, characterized in that the molar ratio of donepezil to hydrochloric acid is 1 to 0.5–5.

7. A process according to claim 4, characterized in that pharmaceutically acceptable solvents are water, acetone, alcohols, a mixture of water with water-miscible solvents.

8. A process for the preparation of an amorphous form of donepezil hydrochloride, characterized in that donepezil hydrochloride is dissolved in a pharmaceutically acceptable solvent or donepezil hydrochloride is prepared *in situ* and the obtained solution is spray-dried.

9. A use of donepezil hydrochloride prepared according to the process of claim 8 for the preparation of a pharmaceutical composition, characterized in that donepezil hydrochloride is dissolved in a pharmaceutically acceptable solvent and the obtained solution is loaded onto a mixture of pharmaceutically acceptable carriers or that donepezyl hydrochloride is directly loaded onto the pharmaceutical composition.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/SI 03/00019

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/445 A61P25/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, MEDLINE, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 46527 A (EISAI CO LTD) 11 December 1997 (1997-12-11) page 53-54, example 57	4,6-9
X	EP 1 027 887 A (PFIZER PROD INC) 16 August 2000 (2000-08-16) '0023!, '0033!, '0042!-'0043!	1-9
A	US 4 610 875 A (CORRIGAN OWEN I ET AL) 9 September 1986 (1986-09-09) column 1, line 56-68; claim 1	1-3,5
A	WO 01 34119 A (ABBOTT LAB) 17 May 2001 (2001-05-17) page 10, line 1 - page 11, line 6	1-3,5

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 September 2003	07/10/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Borst, M

Form PCT/ISA/210 (second sheet) (July 1992)

International Application No
PCT/SI 03/00019

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	BRYSON H M ET AL: "DONEPEZIL" DRUGS AND AGING, ADIS INTERNATIONAL LTD, NZ, vol. 10, no. 3, 1997, pages 234-239, XP000900063 ISSN: 1170-229X the whole document -----	1-9

INTERNATIONAL SEARCH REPORT

International Application No
PCT/SI 03/00019

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 9746527	A	11-12-1997	AT	230396 T	15-01-2003
			AU	1153097 A	05-01-1998
			AU	731282 B2	29-03-2001
			AU	2979297 A	05-01-1998
			CN	1221404 A	30-06-1999
			CZ	9803960 A3	17-03-1999
			DE	69718216 D1	06-02-2003
			DK	1019374 T3	07-04-2003
			EP	1211243 A1	05-06-2002
			EP	1019374 A1	19-07-2000
			ES	2188946 T3	01-07-2003
			WO	9746526 A1	11-12-1997
			WO	9746527 A1	11-12-1997
			JP	10053576 A	24-02-1998
			KR	2000016417 A	25-03-2000
			NO	985721 A	28-01-1999
			NZ	333197 A	30-03-2001
			PL	330362 A1	10-05-1999
			PT	1019374 T	31-03-2003
			RU	2190603 C2	10-10-2002
			SI	9720038 A	30-06-1999
			SK	167698 A3	11-06-1999
			TR	9802531 T2	22-02-1999
			TR	200202374 T2	21-01-2003
			TW	513409 B	11-12-2002
			US	6140321 A	31-10-2000
			US	5985864 A	16-11-1999
			ZA	9705064 A	01-04-1998
			HU	0002270 A2	28-12-2000
EP 1027887	A	16-08-2000	BR	0000359 A	14-08-2001
			EP	1027887 A2	16-08-2000
			JP	2000229888 A	22-08-2000
US 4610875	A	09-09-1986	FR	2525108 A1	21-10-1983
			AR	230183 A1	01-03-1984
			AT	389813 B	12-02-1990
			AT	427282 A	15-07-1989
			AU	555579 B2	02-10-1986
			AU	9043182 A	27-10-1983
			BE	894942 A1	09-05-1983
			CA	1225029 A1	04-08-1987
			CH	655003 A5	27-03-1986
			DE	3241097 A1	20-10-1983
			ES	8505249 A1	01-09-1985
			GB	2119784 A ,B	23-11-1983
			IE	54084 B1	07-06-1989
			IT	1153099 B	14-01-1987
			JP	1677967 C	13-07-1992
			JP	3041444 B	24-06-1991
			JP	58183615 A	26-10-1983
			LU	84468 A1	13-06-1983
			NL	8204461 A	16-11-1983
			PT	75867 A ,B	01-12-1982
			SE	8206697 A	20-10-1983
			US	4769236 A	06-09-1988
WO 0134119	A	17-05-2001	CA	2359945 A1	17-05-2001

INTERNATIONAL SEARCH REPORT

Interna[redacted]al Application No
PCT/SI 03/00019

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0134119 A		EP 1175205 A2	30-01-2002
		JP 2003513904 T	15-04-2003
		WO 0134119 A2	17-05-2001

Form PCT/ISA/210 (patent family annex) (July 1992)